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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/940,227	08/27/2001	Sei-Yu Chen	DEX-0230	4313

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LICATLA & TYRRELL P.C.
66 E. MAIN STREET
MARLTON, NJ 08053

EXAMINER
BLANCHARD, DAVID J

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 09/23/2003

14

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/940,227	Applicant(s) CHEN ET AL.	
	Examin r David J Blanchard	Art Unit 1642	

-- The MAILING DATE f this communication appears on the cover sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9 and 10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. It is acknowledged that the invention of Group VIII was incorrectly drawn to claims 9 and 10 in the restriction requirement in paper #11 mailed 5/19/2003. The examiner intended Group VIII to be drawn to claims 11 and 12 as a method of imaging lung cancer in a patient using an antibody. Applicant is thanked for pointing out the error.

2. Applicant's election with traverse of invention VII claims 9 and 10 in Paper No. 12 is acknowledged. The traversal is on the ground(s) that the inventions are not independent or distinct and that a prior art search would not impose a serious burden on the examiner. The traversal further states that a search relating to an elected nucleic acid, polypeptide, or antibody would reveal references teaching uses for the nucleic acid, polypeptide, or antibody and a search of the nucleic acids or polypeptides or antibodies would be overlapping and thus, would not impose a serious burden on the examiner. This is not found persuasive. The inventions are distinct because as stated in the restriction requirement the products of nucleic acids, polypeptides and antibody are structurally distinct and distinct in functions.

As to the question of burden of search, the antibody of Group VII is classified in class 530, subclass 388.1, the polynucleotides are classified in class 536, subclass 23.1 and the polypeptides are classified in class 530, subclass 300. The divergent

classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not co-extensive and is much more important in evaluating the burden of search. Clearly different searches and different patentability issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is made FINAL.

3. Claims 1-8 and 11-16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction requirement in Paper No. 12 filed on 7/21/03.

4. Claims 9 and 10 are pending and under examination.

Information Disclosure Statement

5. The IDS filed in paper #9 on 10/4/02 contains references AB and AC, which do not contain deposit dates. It is requested that applicant provide the dates for references AB and AC.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

7. Claims 9 and 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claim 9 is indefinite for reciting "specifically binds a cancer cell expressing a polypeptide encoded by an LSG (Lung Specific Gene) comprising SEQ ID NO: 15". It is unclear whether the phrase means the antibody specifically binds the LSG polypeptide encoded by SEQ ID NO: 15 expressed by a cancer cell or binds some other antigen expressed by a cancer cell. Does the antibody bind the polypeptide encoded by SEQ ID NO: 15?

b) Claim 10 is indefinite for reciting "specifically binds a cancer cell expressing a LSG (Lung Specific Gene) polypeptide comprising SEQ ID NO: 83". It is unclear whether the phrase means the antibody specifically binds the LSG polypeptide comprising SEQ ID NO: 83 expressed by a cancer cell or binds some other antigen expressed by a cancer cell. Does the antibody specifically bind the polypeptide of SEQ ID NO: 83?

c) Claim 9 is indefinite for reciting "a polypeptide encoded by a LSG (Lung Specific Gene) comprising SEQ ID NO: 15". How many open reading frames does SEQ ID NO:15 encode? If multiple open reading frames are contemplated in SEQ ID NO: 15, where do they start and end? If a single open reading frame is contemplated by SEQ ID NO: 15, does the open reading frame start at nucleotide #1 or some other nucleotide and where does it end?

d) Claims 9 and 10 are indefinite for reciting "Gene". The claim is drawn to a "gene" encoding a target antigen. According to Genes IV (Lewin et al, Oxford University Press, page 810, 1990), a gene is defined as "the segment of DNA involved in producing a polypeptide chain; it includes regions preceding and following the coding regions (leader and trailer) as well as intervening sequences (introns) between individual coding segments (exons)". From the teachings of the specification, however, the nucleic acid sequences introducing an antigen appear limited to the specific coding regions, and do not include expression control elements that fall under the definition of a gene. Accordingly, the claim is indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 9 and 10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 9 and 10 are broadly drawn to a large genus of nucleic acid molecules and members of the genus are variable because of the potentiality of the many different proteins they may encode. Therefore, many structurally unrelated DNAs are encompassed within the scope of these claims, including partial DNA sequences. Applicants' disclosure fails to describe any cDNAs that correspond to SEQ ID NO: 15, nor is it clear that the resulting sequences would be full-length. The sequence prepared from undefined parts of a cDNA clone may not comprise the entire coding region of any particular gene, nor is it clear that partial sequences would even be in frame to encode a lung specific gene polypeptide. The claims, as written encompass polynucleotides, which vary substantially in length and also in nucleotide composition. The specification does not contain any disclosure of the function of a full-length open reading frame (ORF) that includes SEQ ID NO: 15. Further, the specification does not describe any of the structural elements of a gene that would encode these cDNA sequences. For example, the specification does not describe the organization, location or actual DNA sequences of promoter and regulatory regions and introns, all defining elements of a "gene". The specification lacks information to lead one of skill in the art to understand that the applicant had possession of the broadly claimed invention at the time the instant application was filed. Thus, one of skill in the art would not understand that the applicant had possession of the claimed invention at the time the instant application was filed.

10. Claims 9 and 10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detecting differentially expressed mRNA of SEQ

ID NO: 15 in lung cancer cells, does not reasonably provide enablement for antibodies that bind a cancer cell expressing a "lung specific gene" polypeptide encoded by SEQ ID NO: 15 or a cancer cell expressing a lung specific polypeptide as set forth in SEQ ID NO: 83 or differentially expressed mRNA that encodes the polypeptide of SEQ ID NO: 83. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to antibodies that bind a cancer cell expressing a "lung specific gene" polypeptide encoded by SEQ ID NO: 15 or the "lung specific gene" polypeptide as set forth in SEQ ID NO: 83. The specification teaches that "Lng140" encoded by SEQ ID NO: 15 is expressed in a lung-specific manner (see Example 15 and Table 1 on page 140), and shows that mRNA expression of "Lng140" is upregulated or overexpressed in 20 lung cancer tissues compared to their normal adjacent tissue in 38 cancer matching pairs (see example 15 and Table 2, lung tissue samples #1, 3, 6, 8, 9, 12, 13, 16, 20, 22, 24-27, 29-32, 34 and 38). The specification

does not teach that the polypeptide encoded by SEQ ID NO: 15 or the polypeptide of SEQ ID NO: 83 are expressed in cancer cells. Further, the specification does not teach that the mRNA encoding SEQ ID NO: 83 is expressed or differentially expressed in a cancer cell, nor does it teach that SEQ ID NO: 83 is expressed or that protein translation of SEQ ID NO: 83 is upregulated in a cancer cell. The specification does not reasonably provide enablement for using an antibody to detect the presence or absence of a "Lng140" polypeptide encoded by SEQ ID NO: 15 expressed by a cancer cell. Likewise, the specification does not reasonably provide enablement for using an antibody to detect the presence or absence of the polypeptide set forth in SEQ ID NO: 83 expressed by a cancer cell, nor does it provide enablement for detecting the mRNA that encodes SEQ ID NO; 83.

Those of skill in the art recognize that expression of mRNA, specific for a tissue type, does not necessarily correlate nor predict equivalent levels of polypeptide expression. In fact, evidence abounds in which protein levels do not correlate with steady-state mRNA levels or alterations in mRNA levels. For example, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Further, Powell et al (Pharmacogenetics, 1998, Vol. 8, pp. 411-421, abstract) teach that mRNA levels for cytochrome P450 E1 did not correlate with the level of corresponding protein, and conclude that the regulation of said protein is highly complex. Vallejo et al (Biochimie, 2000, vol. 82, pp. 1129-1133, abstract) teach that no correlation was found

between NRF-2 mRNA and protein levels suggesting post-transcriptional regulation of NRF-2 protein levels. These references serve to demonstrate that the analysis of levels of polynucleotide transcripts cannot be relied upon to anticipate levels of protein expression. Further, Jang et al (Clinical and Experimental Metastasis, 1997, vol. 15, pp. 469-483, abstract) teach that further studies are necessary to determine if changes in protein levels track with changes in mRNA levels for metastasis associated genes in murine tumor cells, thus providing further evidence that one of skill in the art cannot anticipate that the level of a specific mRNA expressed by a cell will be paralleled at the protein level due to complex homeostatic factors controlling translation and post-translational modification.

Thus, the predictability of protein translation and its possible utility as a diagnostic are not necessarily contingent on the levels of mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. Therefore, absent evidence of "Lng140" (SEQ ID NO:15) or SEQ ID NO: 83 protein expression, including the correlation to a diseased state, one of skill in the art would be unable to predictably use the "Lng140" polypeptide encoded by SEQ ID NO: 15 or the polypeptide set forth in SEQ ID NO: 83 in any diagnostic setting without undue experimentation. The specification does not predict or teach whether the "Lng140" polypeptide or the polypeptide set forth in SEQ ID NO; 83 would be overexpressed or underexpressed in a specific, diseased tissue compared to the healthy tissue control. In the absence of a direct correlation between the upregulation of transcription and translation of the "Lng140" polypeptide or the polypeptide of SEQ ID NO: 83 associated with a disease

state, one of ordinary skill in the art would be unable to use an antibody specific for "Lng140" or SEQ ID NO: 83 to bind a cancer cell.

Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed antibodies in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970).

In view of the lack of predictability in the art as evidenced by Fu et al., Powell et al., Vallejo et al., and Jang et al., and the lack of examples in the specification, and lack of guidance in the specification related to antibodies that bind a cancer cell expressing a lung specific gene polypeptide encoded by SEQ ID NO: 15 or a lung specific gene polypeptide as set forth in SEQ ID NO: 83, one skilled in the art would be forced into undue experimentation in order to practice the claimed invention.

Conclusion

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Blanchard, whose telephone number is (703) 605-1200. The examiner can normally be reached on Monday through Friday from 8:00 am to 4:30 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,
David Blanchard.
703-605-1200

LARRY R. HELMS, PH.D
PRIMARY EXAMINER